charles river

Reproductive and Juvenile Toxicology

Historical Control Data in Rabbits

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[1] **Additional HCD endpoints and years are available upon request.**

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP MATERNAL FINDINGS			
Parameter	Total	Minimum*	Maximum*
No. of Does Inseminated / Mated	1512	20	25
No. of Does Pregnant	1447	17	22
No. of Does Pregnant by Ammonium Sulfide Staining	1	0	1
No. of Does with Abortion	7	0	1
Abortion Rate (%)	-	0.0	5.0
No. of Does Littering Early	0	0	0
No. of Does with Live Fetuses	1425	16	22
No. of Does with Total Litter Death / Resorption	8	0	2
No. of Does Dying or Unscheduled Euthanasia on Study	13	0	2
Mortality Rate (%)	-	0.0	9.1
Pregnancy Rate (%)	-	81.8	100.0

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP OVARIAN AND UTERINE FINDINGS			
Parameter	Average	Minimum*	Maximum*
Corpora Lutea / Doe	9.8	8.4	11.4
Total Implantation Sites / Litter	8.8	7.7	10.1
Sex Ratio (% Males) / Litter	48.9	39.9	58.3
Total Live Fetuses / Litter	8.5	6.9	9.7
Dead Fetuses / Litter	0.01	0.0	0.3
Early Resorptions / Litter	0.25	0.0	0.7
Late Resorptions / Litter	0.11	0.0	0.5
Total Resorptions / Litter	0.35	0.0	0.8
Pre-Implantation Loss (%) / Litter	9.5	3.1	18.2
Post-Implantation Loss (%) / Litter	3.9	0.6	11.5

* Study ranges, based on the group incidence, group percentage or group mean

[@] The year (s) dosing was initiated on the studies

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EMBRYO-FETAL DEVELOPMENT STUDIES			
FETAL WEIGHTS - SUMMARY DATA			
Parameter	Average	Minimum*	Maximum*
Fetal Weight (g) - Males	43.4	40.1	47.9
Fetal Weight (g) - Females	42.3	38.4	46.4
Fetal Weight (g) - Total	42.9	39.5	47.1

* Study ranges, based on the group incidence, group percentage or group mean

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HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
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EMBRYO-FETAL DEVELOPMENT STUDIES

GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS
MALFORMATIONS AND VARIATIONS

	Litters examined	
EXTERNAL (EXT)	1422	Total no. of
VISCERAL (VIS)	1422	studies/groups used
SKELETAL (SKE)	1422	71
TECHNIQUE OF WILSON (WT)	19	

	Litters affected			
MALFORMATIONS	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Exencephaly (EXT,WT,SKE)	2	0.14	0.00	4.76
Cranium: Cleft palate (EXT,WT)	2	0.14	0.00	5.26
Brain: Anencephaly (VIS)	1	0.07	0.00	4.55
Brain: Hydrocephaly (EXT,VIS,WT)	5	0.35	0.00	5.26
Brain: Hemorrhagic cerebrum (VIS)	1	0.07	0.00	4.76
Brain: Cerebrum, Small (VIS)	2	0.14	0.00	5.26
Skull: Interparietal bone(s): Absent (SKE)	1	0.07	0.00	4.76
Skull: Supraoccipital bone: Absent (SKE)	1	0.07	0.00	4.76
Skull: Premaxilla bone(s): Fused (SKE)	1	0.07	0.00	5.00
Skull: Zygomatic arch: Absent (SKE)	1	0.07	0.00	4.76
Eye(s): Eye(s)/Bulge(s) small (microphthalmia) (EXT)	6	0.42	0.00	5.00
Eye(s): Eye(s)/Bulge(s) malpositioned) (EXT)	1	0.07	0.00	4.76
Eye(s): Open (EXT,WT)	2	0.14	0.00	4.76
Eye(s): Opacity (EXT)	1	0.07	0.00	4.55
Nasal bone(s): Fused (SKE) ‡	1	0.07	0.00	5.00
Ear(s): Pinna, Malpositioned (EXT)	1	0.07	0.00	4.55
Face: Naris, Small (EXT)	1	0.07	0.00	5.00
Face: Tooth, Not erupted (EXT)	1	0.07	0.00	5.00
Face: Naris, Malpositioned (EXT)	1	0.07	0.00	5.00
Face: Upper jaw reduced (micrognathia) (EXT,VIS,SKE)	1	0.07	0.00	5.00
Heart: Dilatation of the ascending aorta (VIS)	8	0.56	0.00	10.53
Heart: Dilatation of the descending aorta (VIS)	3	0.21	0.00	5.00
Heart: Dilatation of aortic arch (VIS)	5	0.35	0.00	5.56
Heart: Major vessels: pulmonary trunk stenosed (VIS)	6	0.42	0.00	10.53
Heart: Subclavian artery absent (VIS)	1	0.07	0.00	4.55
Heart: Minor vessels variation: retroesophageal subclavian artery (VIS)	14	0.98	0.00	10.00
Heart: Ventricular septum absent (VIS)	4	0.28	0.00	5.00
Heart: Atrium absent (VIS)	1	0.07	0.00	4.76
Heart: Ventricular septum defect (VIS)	9	0.63	0.00	11.11
Heart: Ventricular wall, Thick (VIS)	1	0.07	0.00	5.00
Heart: Persistent truncus arteriosus (Common truncus) (VIS)	4	0.28	0.00	5.00

* Study ranges, based on the group incidence
‡ Regraded in 2017

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Heart: Globular (VIS)	2	0.14	0.00	5.00
Heart: Misshapen (VIS)	4	0.28	0.00	9.52
Heart: Major vessels: aorta dilated (VIS)	2	0.14	0.00	5.56
Heart: Major vessels: aortic arch absent (VIS)	4	0.28	0.00	16.67
Heart: Minor vessels: left subclavian merges into pulmonary artery (VIS)	1	0.07	0.00	5.56
Heart: Right-sided aorta (VIS)	1	0.07	0.00	5.00
Heart: Enlarged (VIS)	1	0.07	0.00	5.00
Heart: Papillary muscle flaccid/reduced (VIS)	1	0.07	0.00	5.56
Heart: Bicuspid valves absent (VIS)	3	0.21	0.00	5.56
Heart: Rotation/malpositioned (VIS)	1	0.07	0.00	4.76
Heart: Cordae tendinae absent (VIS)	1	0.07	0.00	4.76
Heart: Papillary muscles absent (VIS)	1	0.07	0.00	4.76
Heart: Semilunar valves at pulmonary trunk absent (VIS)	1	0.07	0.00	5.00
Heart: Pericardium, Blood filled (VIS)	4	0.28	0.00	5.56
Lungs and Thymus: Lung lobe(s) small/reduced (VIS)	4	0.28	0.00	4.76
Lungs: Enlarged lung lobes (VIS)	1	0.07	0.00	5.00
Lungs: Lung malpositioned (VIS)	1	0.07	0.00	4.55
Lungs: Lung small (VIS)	1	0.07	0.00	4.55
Lungs: Lung lobes fused (VIS) ‡‡	3	0.21	0.00	5.00
Vertebral column: Scoliosis/kyphosis/lordosis (SKE)	1	0.07	0.00	4.55
Vertebral column: Cervical vertebral centrum: Absent (SKE) ‡	2	0.14	0.00	5.56
Vertebral column: Cervical vertebral arch(es): Absent (SKE) ‡	3	0.21	0.00	5.56
Vertebral column: Cervical vertebral centra: Fused (SKE)	2	0.14	0.00	5.26
Vertebral column: Thoracic vertebral centra: Fused (SKE)	6	0.42	0.00	5.88
Vertebral column: Lumbar vertebral centra: Fused (SKE) ‡	2	0.14	0.00	5.00
Vertebral column: Thoracic vertebral centrum: Absent (SKE)	5	0.35	0.00	5.26
Vertebral column: Lumbar vertebra(e): Absent (SKE)	1	0.07	0.00	4.76
Vertebral column: Lumbar vertebral arch(es): Absent/unossified (SKE)	6	0.42	0.00	9.09
Vertebral column: Thoracic vertebral arch(es): Fused (SKE)	4	0.28	0.00	5.88
Vertebral column: Thoracic vertebral arch(es): Absent (SKE)	12	0.84	0.00	5.88
Spleen: Absent (VIS)	1	0.07	0.00	4.55
Ribs: Fused (SKE)	7	0.49	0.00	5.88
Ribs: Absent (SKE)	7	0.49	0.00	5.26
Ribs: Branched (SKE) ‡‡	2	0.14	0.00	5.26
Thorax: Thoracoschisis (EXT)	1	0.07	0.00	4.76
Thoracic cavity: Situs inversus (VIS)	1	0.07	0.00	4.55

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‡ Regraded in 2017
‡‡ Regraded in 2018

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Abdomen: Abdominal muscles herniated (EXT)	4	0.28	0.00	5.00
Abdomen: Abdominal herniation/ eventration of intestines and/or liver (gastrochisis) (EXT,VIS)	4	0.28	0.00	5.56
Abdominal cavity: Stomach malpositioned (VIS)	1	0.07	0.00	4.55
Abdomen: Intestines protruding at umbilicus (omphalocele) (EXT)	3	0.21	0.00	5.26
Abdominal cavity: Intestines malpositioned (VIS)	1	0.07	0.00	4.55
Abdominal cavity: Intestine, Interrupted (VIS)	1	0.07	0.00	5.00
Abdominal cavity/Diaphragm: Diaphragmatic hernia (VIS)	7	0.49	0.00	9.52
Abdominal cavity: Hermaphroditism (VIS)	1	0.07	0.00	4.55
Abdominal cavity: Pancreas absent (VIS)	1	0.07	0.00	5.56
Abdominal cavity: Abdominal cavity red fluid filled (VIS)	1	0.07	0.00	4.55
Abdominal cavity: Thoracic cavity red fluid filled (VIS)	1	0.07	0.00	4.55
Anus: Absent (Anal atresia) (EXT)	1	0.07	0.00	5.00
Liver: Supernumerary lobe(s) (VIS)	6	0.42	0.00	10.53
Liver: Small lobe(s) (VIS) ‡	1	0.07	0.00	4.55
Liver: Large, severe (VIS)	1	0.07	0.00	4.76
Liver: Lobe(s) fused (VIS)	3	0.21	0.00	5.00
Liver: Misshapen (VIS)	1	0.07	0.00	4.55
Kidney(s): Reduced severely (VIS)	1	0.07	0.00	5.00
Kidney(s): Absent (VIS)	1	0.07	0.00	5.00
Kidney(s): Fused (VIS)	1	0.07	0.00	5.00
Kidney(s): Multiple variants in kidneys and ureters (VIS)	1	0.07	0.00	5.00
Kidney(s): Renal papilla(e), small, severe (VIS)	1	0.07	0.00	4.76
Kidney(s): Misshapen (VIS)	1	0.07	0.00	5.26
Kidney(s): Malpositioned (VIS) ‡‡	6	0.42	0.00	5.26
Urinary Bladder: Misshapen (VIS)	1	0.07	0.00	4.76
Ureter(s): Absent (VIS)	1	0.07	0.00	5.00
Tail: Microcaudia (EXT)	2	0.14	0.00	5.00
Limb(s): Brachydactyly (EXT)	2	0.14	0.00	5.00
Limb(s): Syndactyly (EXT)	1	0.07	0.00	4.76
Limb(s): Abnormal flexure/hyperflexure/articulation of forelimb(s) (EXT)	1	0.07	0.00	4.55
Limb(s): Abnormal flexure/hyperflexure/hyperextension of hindlimb(s) (EXT)	1	0.07	0.00	4.55
Limb(s): Abnormal flexure/hyperflexure of forepaw(s) (EXT)	4	0.28	0.00	5.26
Limb(s): Abnormal flexure of hindpaw(s) (EXT)	1	0.07	0.00	4.76
Limb(s): Hindlimb(s), Large (Macromelia) (EXT)	1	0.07	0.00	4.55

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‡ Regraded in 2017
‡‡ Regraded in 2018

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RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES

GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS
MALFORMATIONS AND VARIATIONS

	Litters affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Limb(s): Forelimb malrotated (EXT)	2	0.14	0.00	5.26
Limb(s): Short tibia (SKE)	1	0.07	0.00	4.76
Sternebra: Sternoschisis (SKE)	1	0.07	0.00	4.76
Scapula(e): Scapula body small (SKE)	1	0.07	0.00	4.55
Gross Exam: Cleft in skin at sacral region (EXT)	1	0.07	0.00	5.00
General: Skin, lesion (EXT)	1	0.07	0.00	4.55
General: Entire body, Subcutaneous hemorrhage (EXT)	1	0.07	0.00	4.55
Fat Pad: Accentuated entire body (EXT)	2	0.14	0.00	4.55

* Study ranges, based on the group incidence

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters examined			
EXTERNAL (EXT)	1422	Total no. of		
VISCERAL (VIS)	1422	studies/groups used		
TECHNIQUE OF WILSON (WT)	19	71		
EXTERNAL AND VISCERAL	Litters affected			
VARIATIONS	SUM	AVERAGE %	MIN %*	MAX %*
Brain: Perimeningeal space, Red material (VIS)	1	0.07	0.00	5.26
Brain: Moderate dilation of lateral/third ventricles (VIS,WT)	3	0.21	0.00	5.26
Eye(s): Circumcornial hemorrhage (EXT)	8	0.56	0.00	10.00
Heart: Minor vessels: left common carotid merges into innominate (VIS)	1	0.07	0.00	5.56
Heart: Minor vessels; carotid/subclavian arteries arises from/merges into innominate artery (VIS)	1	0.07	0.00	4.76
Heart: Minor vessels; carotid/subclavian/innominate arteries merge into aortic arch/ascending aorta (VIS)	1	0.07	0.00	5.00
Heart: Minor vessels; extra vessel (VIS)	38	2.67	0.00	50.00
Heart: Minor vessels; innominate artery absent (VIS)	7	0.49	0.00	10.00
Heart: Minor vessels variation: malpositioned subclavian (VIS)	2	0.14	0.00	6.25
Heart: Subclavian narrowed (VIS)	1	0.07	0.00	4.55
Heart: Ventricle large (VIS)	1	0.07	0.00	4.76
Heart: Ventricle small (VIS) ‡‡	2	0.14	0.00	5.56
Lungs: Azygos/accessory lobe absent (VIS)	137	9.63	0.00	35.00
Lungs: Accessory lobe reduced (VIS)	1	0.07	0.00	4.55
Lungs: Cyst on accessory lobe (VIS)	1	0.07	0.00	4.55
Spleen: Reduced (VIS)	4	0.28	0.00	11.11
Spleen: Supernumerary (VIS)	2	0.14	0.00	4.76
Spleen: Discoloration (VIS)	1	0.07	0.00	4.55
Pancreas: Reduced (VIS)	1	0.07	0.00	5.56
Gallbladder: Absent (VIS)	21	1.48	0.00	10.00
Gallbladder: Small/Reduced (VIS)	2	0.14	0.00	5.26
Gallbladder: Supernumerary (VIS)	5	0.35	0.00	5.88
Liver: Lobe, Additional fissure (VIS)	3	0.21	0.00	5.26
Liver: Vestigial lobe (VIS)	23	1.62	0.00	28.57
Liver: Cyst (VIS)	1	0.07	0.00	5.00
Kidney(s): Pelvic kidney(s) (VIS)	2	0.14	0.00	5.26
Kidney(s): Absence of renal papillae (VIS)	2	0.14	0.00	5.00
Kidney(s): Renal papilla(e) small (VIS)	3	0.21	0.00	5.56
Kidney(s): Abnormal consistency solid white (VIS)	1	0.07	0.00	5.00

* Study ranges, based on the group incidence

‡‡ Regraded in 2018

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RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
EXTERNAL AND VISCERAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Adrenal gland: Accessory adrenal nodule present (VIS)	1	0.07	0.00	5.26
Abdomen: Abdominal distention (EXT)	1	0.07	0.00	4.55
Abdominal cavity: Cyst (VIS)	1	0.07	0.00	5.26
Abdominal/thoracic cavity: Excessive fluid present (ascites) (VIS)	1	0.07	0.00	4.76
Abdomen: Malpositioned umbilicus (EXT)	1	0.07	0.00	4.76
Testes: Cyst (VIS)	1	0.07	0.00	5.00
Urinary bladder: Distended (VIS)	1	0.07	0.00	5.00
Vein: Renal vein(s), Supernumerary (VIS)	4	0.28	0.00	19.05
Ureter(s): Retrocaval (VIS)	73	5.13	0.00	31.58
Ureter(s): Abnormal consistency solid white (VIS)	1	0.07	0.00	5.00
Ovary(ies): Cyst (VIS)	4	0.28	0.00	10.00
Tail: Kinked (EXT)	1	0.07	0.00	5.00
Gross exam: Subcutaneous edema (EXT)	2	0.14	0.00	4.76

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Litters examined 1422		Total no. of studies/groups used 71	
	Litters affected			
SKELETAL VARIATIONS	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Hyoid bone: Incomplete ossification	534	37.55	0.00	85.71
[Hyoid bone: Irregular ossification]	22	1.55	0.00	25.00
Hyoid bone: Irregular ossification (misshapen)	174	12.24	0.00	40.00
Hyoid bone: Unossified [absent]	27	1.90	0.00	11.11
Hyoid bone: Bipartite	12	0.84	0.00	14.29
Hyoid bone: Semi-bipartite	42	2.95	0.00	59.09
Hyoid bone ala(e): Bent	109	7.67	0.00	45.00
Frontal bone(s): Incomplete ossification	555	39.03	0.00	95.00
[Frontal bone(s): Irregular ossification]	1	0.07	0.00	5.56
Frontal bone(s): Fusion	3	0.21	0.00	5.26
Frontal/parietal bone(s): Unossified line	158	11.11	0.00	100.00
Frontal bone(s): Unossified area	2	0.14	0.00	4.76
Frontal bone(s): Misshapen	5	0.35	0.00	9.52
Frontal bone(s): Large	1	0.07	0.00	4.55
Parietal bone(s): Incomplete ossification	26	1.83	0.00	18.18
Parietal bone(s): Unossified area	1	0.07	0.00	4.55
Parietal bone(s): Misshapen	2	0.14	0.00	4.76
Parietal bone(s): Large	1	0.07	0.00	4.55
Interparietal bones: Incomplete ossification	10	0.70	0.00	11.76
Interparietal bones: Increased ossification	1	0.07	0.00	4.55
Interparietal bones: Malpositioned	1	0.07	0.00	4.55
Supraoccipital bone: Malpositioned	1	0.07	0.00	4.55
Supraoccipital bone: Reduced ossification	2	0.14	0.00	5.88
Supraoccipital bone: Incomplete ossification	4	0.28	0.00	15.00
Squamosal bone(s): Incomplete ossification	1	0.07	0.00	4.76
Nasal bone(s): Incomplete ossification [irregular]	45	3.16	0.00	21.05
Nasal bone and frontal bone: Fused, partial	2	0.14	0.00	5.00
Nasal bone(s): Unossified line	11	0.77	0.00	10.53
Nasal bone: Misshapen	2	0.14	0.00	4.76
Nasal bone: Suture, Malpositioned	1	0.07	0.00	4.55
Maxilla: Single incisor socket	1	0.07	0.00	5.00
Premaxilla: Incomplete ossification	2	0.14	0.00	5.00

* Study ranges, based on the group incidence

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CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN				
Thoracic vertebral centrum: Incomplete ossification	13	0.91	0.00	11.11
Thoracic vertebral centrum: Semi-bipartite/dumbbell	496	34.88	0.00	63.16
Thoracic vertebral centrum: Bipartite	6	0.42	0.00	5.56
Thoracic vertebral centrum: Misaligned (includes malpositioned, displaced)	13	0.91	0.00	9.09
Thoracic vertebral centrum: Unossified	3	0.21	0.00	5.56
Thoracic vertebral centrum: Misshapen	2	0.14	0.00	4.76
Thoracic vertebral arch(es): Incomplete/reduced ossification	8	0.56	0.00	5.56
Thoracic vertebral arch(es): Ossification center	6	0.42	0.00	10.00
Caudal vertebra(e): Reduced no.	19	1.34	0.00	15.00
Caudal vertebra(e): Incomplete ossification	10	0.70	0.00	9.09
Caudal vertebra(e): Misaligned (includes malpositioned, displaced)	20	1.41	0.00	13.64
Caudal vertebra(e): Fused	3	0.21	0.00	5.00
Caudal vertebra(e): Bipartite	5	0.35	0.00	5.26
Cervical vertebra (1st): Incomplete ossification	22	1.55	0.00	35.29
Cervical vertebra (1st): Misshapen	1	0.07	0.00	5.26
Cervical vertebra: Ossification center	3	0.21	0.00	10.00
Cervical vertebral centrum: Misaligned (includes malpositioned)	5	0.35	0.00	5.56
Cervical vertebral centrum: Semi-bipartite/dumbbell	3	0.21	0.00	5.56
Cervical vertebral centrum: Bipartite	1	0.07	0.00	4.76
Cervical vertebral centrum: Incomplete/reduced ossification	27	1.90	0.00	27.27
Cervical vertebral centrum: Misshapen	1	0.07	0.00	4.76
Cervical vertebral centrum: Irregular ossification	1	0.07	0.00	5.00
Cervical vertebral arch(es): Incomplete/reduced ossification	4	0.28	0.00	5.56
Cervical vertebral arch(es): Unossified	1	0.07	0.00	4.76
Cervical vertebra arch(es): Ossification center	7	0.49	0.00	10.00
Lumbar vertebra: Ossification center	12	0.84	0.00	18.18
Lumbar vertebral centrum: Misaligned (includes malpositioned)	5	0.35	0.00	9.09
Lumbar vertebral arch(es): Incomplete ossification	1	0.07	0.00	4.76
Lumbar vertebral arch(es): Irregular ossification	1	0.07	0.00	4.76
Lumbar vertebral arch(es): Misaligned	1	0.07	0.00	5.88
Lumbar vertebral arch(es): Ossification center	10	0.70	0.00	13.64
Lumbar vertebral centrum: Absent	1	0.07	0.00	5.88
Lumbar vertebral centrum: Bipartite	1	0.07	0.00	4.76
Lumbar vertebral centrum: Semi-bipartite	1	0.07	0.00	4.76
Lumbar vertebral centrum: Incomplete ossification	2	0.14	0.00	4.76
1st Lumbar centrum fused with 13th thoracic centrum	1	0.07	0.00	4.76

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CONT'D)				
Sacral vertebral centrum: Incomplete ossification	1	0.07	0.00	5.00
Sacral vertebra(e): Irregular ossification	1	0.07	0.00	4.76
Sacral vertebral arch(es): Incomplete ossification	3	0.21	0.00	10.00
Extra pre-sacral vertebrae	26	1.83	0.00	15.79
25 pre-sacral vertebrae	9	0.63	0.00	10.00
Ossification center(s) on 1st lumbar vertebra	38	2.67	0.00	15.79
RIBS				
Nodulated	20	1.41	0.00	15.00
Reduced (Incomplete ossification)	8	0.56	0.00	10.00
Bifurcated	1	0.07	0.00	4.55
Misaligned (displaced)	1	0.07	0.00	5.26
Misshapen	2	0.14	0.00	5.26
Short	1	0.07	0.00	5.00
Cervical, Full	2	0.14	0.00	5.26
Cervical, Short	10	0.70	0.00	15.00
Ossification center(s) on 7th cervical vertebra	53	3.73	0.00	30.00
Rib(s) on 7th cervical vertebra	51	3.59	0.00	16.67
Malpositioned	1	0.07	0.00	4.76
Ossification center(s) on 1st cervical vertebra	1	0.07	0.00	5.26
Interrupted rib(s)	5	0.35	0.00	5.88
Rib 13th, full (extra) (unilateral/bilateral)	274	19.27	0.00	100.00
Rib 13th, short (rudimentary) (unilateral/bilateral)	241	16.95	0.00	90.91
STERNEBRAL COLUMN				
Fused	135	9.49	0.00	25.00
Misaligned	5	0.35	0.00	5.00
Extra sternebra(e)/extra ossification in sternebral column	151	10.62	0.00	35.29
Bifurcated/misshapen	26	1.83	0.00	47.62
Incomplete ossification	279	19.62	0.00	100.00
Increased ossification	1	0.07	0.00	4.55
Unossified	207	14.56	0.00	94.44
Bipartite ossification	36	2.53	0.00	36.36
Dumbbell ossification /semi-bipartite	15	1.05	0.00	21.05
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	80	5.63	0.00	30.00
Pubic bone(s): Absent/unossified	7	0.49	0.00	5.56
LIMBS				
Scapula(e): Misshapen	1	0.07	0.00	4.55
Reduced no. of phalange(s) in pollex(ices)	8	0.56	0.00	5.26
Reduced no. of tarsal bones	2	0.14	0.00	5.00
Reduced no. of bones in forepaw(s)	2	0.14	0.00	4.76

* Study ranges, based on the group incidence

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
LIMBS (CONT'D)				
Reduced no. of phalange(s) in forepaw(s)	10	0.70	0.00	10.00
Reduced no. of phalange(s) in hindpaw(s)	1	0.07	0.00	5.00
Forepaw(s): Phalange(s) misshapen	2	0.14	0.00	5.56
Clavicle(s): Incomplete ossification	1	0.07	0.00	5.00
Hindpaw(s): Irregular ossification	5	0.35	0.00	5.56
Forepaw(s): Irregular ossification	19	1.34	0.00	22.22
Forepaw(s): Phalange(s) incomplete ossification	3	0.21	0.00	5.26
Hindlimb: Tarsal bone increased ossification	1	0.07	0.00	4.76
Hindlimb: Tarsal bone unossified	2	0.14	0.00	9.52
Hindlimb: Tarsal bone incomplete ossification	7	0.49	0.00	19.05
Forelimb: Ulna thin	1	0.07	0.00	4.55

* Study ranges, based on the group incidence

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HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES

GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS
MALFORMATIONS AND VARIATIONS

	Fetuses examined	
EXTERNAL (EXT)	12047	Total no. of
VISCERAL (VIS)	12046	studies/groups used
SKELETAL (SKE)	12045	71
TECHNIQUE OF WILSON (WT)	75	

	Fetuses affected			
MALFORMATIONS	SUM	AVERAGE %	MIN %*	MAX %*
Cranium: Exencephaly (EXT,WT,SKE)	2	0.02	0.00	0.61
Cranium: Cleft palate (EXT,WT)	2	0.02	0.00	0.66
Brain: Anencephaly (VIS)	1	0.01	0.00	0.55
Brain: Hydrocephaly (EXT,VIS,WT)	7	0.06	0.00	1.90
Brain: Hemorrhagic cerebrum (VIS)	2	0.02	0.00	1.09
Brain: Cerebrum, Small (VIS)	2	0.02	0.00	0.57
Skull: Interparietal bone(s): Absent (SKE)	1	0.01	0.00	0.57
Skull: Supraoccipital bone: Absent (SKE)	1	0.01	0.00	0.57
Skull: Premaxilla bone(s): Fused (SKE)	1	0.01	0.00	0.53
Skull: Zygomatic arch: Absent (SKE)	1	0.01	0.00	0.57
Eye(s): Eye(s)/Bulge(s) small (microphthalmia) (EXT)	6	0.05	0.00	0.61
Eye(s): Eye(s)/Bulge(s) malpositioned) (EXT)	1	0.01	0.00	0.57
Eye(s): Open (EXT,WT)	2	0.02	0.00	0.61
Eye(s): Opacity (EXT)	1	0.01	0.00	0.52
Nasal bone(s): Fused (SKE) ‡	1	0.01	0.00	0.53
Ear(s): Pinna, Malpositioned (EXT)	1	0.01	0.00	0.55
Face: Naris, Small (EXT)	1	0.01	0.00	0.53
Face: Tooth, Not erupted (EXT)	1	0.01	0.00	0.53
Face: Naris, Malpositioned (EXT)	1	0.01	0.00	0.53
Face: Upper jaw reduced (micrognathia) (EXT,VIS,SKE)	1	0.01	0.00	0.53
Heart: Dilatation of the ascending aorta (VIS)	8	0.07	0.00	1.20
Heart: Dilatation of the descending aorta (VIS)	3	0.02	0.00	0.61
Heart: Dilatation of aortic arch (VIS)	5	0.04	0.00	0.68
Heart: Major vessels: pulmonary trunk stenosed (VIS)	6	0.05	0.00	1.20
Heart: Subclavian artery absent (VIS)	1	0.01	0.00	0.55
Heart: Minor vessels variation: retroesophageal subclavian artery (VIS)	18	0.15	0.00	2.43
Heart: Ventricular septum absent (VIS)	4	0.03	0.00	0.62
Heart: Atrium absent (VIS)	1	0.01	0.00	0.52
Heart: Ventricular septum defect (VIS)	9	0.07	0.00	1.35
Heart: Ventricular wall, Thick (VIS)	1	0.01	0.00	0.62
Heart: Persistent truncus arteriosus (Common truncus) (VIS)	4	0.03	0.00	0.62
Heart: Globular (VIS)	2	0.02	0.00	0.58

* Study ranges, based on the group incidence
‡ Regraded in 2017

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Heart: Misshapen (VIS)	6	0.05	0.00	2.30
Heart: Major vessels: aorta dilated (VIS)	2	0.02	0.00	0.62
Heart: Major vessels: aortic arch absent (VIS)	5	0.04	0.00	2.40
Heart: Minor vessels: left subclavian merges into pulmonary artery (VIS)	1	0.01	0.00	0.62
Heart: Right-sided aorta (VIS)	1	0.01	0.00	0.58
Heart: Enlarged (VIS)	1	0.01	0.00	0.62
Heart: Papillary muscle flaccid/reduced (VIS)	1	0.01	0.00	0.68
Heart: Bicuspid valves absent (VIS)	3	0.02	0.00	0.68
Heart: Rotation/malpositioned (VIS)	1	0.01	0.00	0.61
Heart: Cordae tendinae absent (VIS)	1	0.01	0.00	0.61
Heart: Papillary muscles absent (VIS)	1	0.01	0.00	0.61
Heart: Semilunar valves at pulmonary trunk absent (VIS)	1	0.01	0.00	0.61
Heart: Pericardium, Blood filled (VIS)	5	0.04	0.00	1.20
Lungs and Thymus: Lung lobe(s) small/reduced (VIS)	4	0.03	0.00	0.59
Lungs: Enlarged lung lobes (VIS)	1	0.01	0.00	0.57
Lungs: Lung malpositioned (VIS)	1	0.01	0.00	0.55
Lungs: Lung small (VIS)	1	0.01	0.00	0.55
Lungs: Lung lobes fused (VIS) ‡‡	3	0.02	0.00	0.56
Vertebral column: Scoliosis/kyphosis/lordosis (SKE)	1	0.01	0.00	0.50
Vertebral column: Cervical vertebral centrum: Absent (SKE) ‡	2	0.02	0.00	0.68
Vertebral column: Cervical vertebral arch(es): Absent (SKE) ‡	3	0.02	0.00	0.68
Vertebral column: Cervical vertebral centra: Fused (SKE)	2	0.02	0.00	0.60
Vertebral column: Thoracic vertebral centra: Fused (SKE)	6	0.05	0.00	0.78
Vertebral column: Lumbar vertebral centra: Fused (SKE) ‡	2	0.02	0.00	0.59
Vertebral column: Thoracic vertebral centrum: Absent (SKE)	5	0.04	0.00	0.70
Vertebral column: Lumbar vertebra(e): Absent (SKE)	1	0.01	0.00	0.57
Vertebral column: Lumbar vertebral arch(es): Absent/unossified(SKE)	6	0.05	0.00	1.08
Vertebral column: Thoracic vertebral arch(es): Fused (SKE)	4	0.03	0.00	0.70
Vertebral column: Thoracic vertebral arch(es): Absent (SKE)	12	0.10	0.00	0.78
Spleen: Absent (VIS)	1	0.01	0.00	0.55
Ribs: Fused (SKE)	8	0.07	0.00	1.20
Ribs: Absent (SKE)	7	0.06	0.00	0.62
Ribs: Branched (SKE) ‡‡	2	0.02	0.00	0.70
Thorax: Thoracoschisis (EXT)	1	0.01	0.00	0.61
Thoracic cavity: Situs inversus (VIS)	1	0.01	0.00	0.55

* Study ranges, based on the group incidence
‡ Regraded in 2017
‡‡ Regraded in 2018

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HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Abdomen: Abdominal muscles herniated (EXT)	4	0.03	0.00	0.61
Abdomen: Abdominal herniation/ eventration of intestines and/or liver (gastrochisis) (EXT,VIS)	4	0.03	0.00	0.68
Abdominal cavity: Stomach malpositioned (VIS)	1	0.01	0.00	0.55
Abdomen: Intestines protruding at umbilicus (omphalocele) (EXT)	3	0.02	0.00	0.56
Abdominal cavity: Intestines malpositioned (VIS)	1	0.01	0.00	0.55
Abdominal cavity: Intestine, Interrupted (VIS)	1	0.01	0.00	0.53
Abdominal cavity/Diaphragm: Diaphragmatic hernia (VIS)	7	0.06	0.00	1.18
Abdominal cavity: Hermaphroditism (VIS)	1	0.01	0.00	0.55
Abdominal cavity: Pancreas absent (VIS)	1	0.01	0.00	0.68
Abdominal cavity: Abdominal cavity red fluid filled (VIS)	1	0.01	0.00	0.52
Abdominal cavity: Thoracic cavity red fluid filled (VIS)	1	0.01	0.00	0.52
Anus: Absent (Anal atresia) (EXT)	1	0.01	0.00	0.53
Liver: Supernumerary lobe(s) (VIS)	6	0.05	0.00	1.11
Liver: Small lobe(s) (VIS) ‡	1	0.01	0.00	0.49
Liver: Large, severe (VIS)	4	0.03	0.00	2.07
Liver: Lobe(s) fused (VIS)	3	0.02	0.00	0.55
Liver: Misshapen (VIS)	1	0.01	0.00	0.54
Kidney(s): Reduced severely (VIS)	2	0.02	0.00	1.23
Kidney(s): Absent (VIS)	1	0.01	0.00	0.52
Kidney(s): Fused (VIS)	2	0.02	0.00	1.23
Kidney(s): Multiple variants in kidneys and ureters (VIS)	1	0.01	0.00	0.61
Kidney(s): Renal papilla(e), small, severe (VIS)	1	0.01	0.00	0.52
Kidney(s): Misshapen (VIS)	1	0.01	0.00	0.58
Kidney(s): Malpositioned (VIS) ‡‡	8	0.07	0.00	1.23
Urinary Bladder: Misshapen (VIS)	1	0.01	0.00	0.52
Ureter(s): Absent (VIS)	1	0.01	0.00	0.52
Tail: Microcaudia (EXT)	2	0.02	0.00	0.55
Limb(s): Brachydactyly (EXT)	2	0.02	0.00	0.61
Limb(s): Syndactyly (EXT)	1	0.01	0.00	0.61
Limb(s): Abnormal flexure/hyperflexure/articulation of forelimb(s) (EXT)	1	0.01	0.00	0.54
Limb(s): Abnormal flexure/hyperflexure/hyperextension of hindlimb(s) (EXT)	1	0.01	0.00	0.49
Limb(s): Abnormal flexure/hyperflexure of forepaw(s) (EXT)	5	0.04	0.00	1.27
Limb(s): Abnormal flexure of hindpaw(s) (EXT)	1	0.01	0.00	0.61
Limb(s): Hindlimb(s), Large (Macromelia) (EXT)	1	0.01	0.00	0.54
Limb(s): Forelimb malrotated (EXT)	2	0.02	0.00	0.58

* Study ranges, based on the group incidence
‡ Regraded in 2017
‡‡ Regraded in 2018

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Limb(s): Short tibia (SKE)	1	0.01	0.00	0.61
Sternebra: Sternoschisis (SKE)	1	0.01	0.00	0.52
Scapula(e): Scapula body small (SKE)	1	0.01	0.00	0.55
Gross Exam: Cleft in skin at sacral region (EXT)	1	0.01	0.00	0.55
General: Skin, lesion (EXT)	1	0.01	0.00	0.55
General: Entire body, Subcutaneous hemorrhage (EXT)	1	0.01	0.00	0.49
Fat Pad: Accentuated entire body (EXT)	2	0.02	0.00	0.55

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses examined			
EXTERNAL (EXT)	12047			
VISCERAL (VIS)	12046	Total no. of studies/groups used		
TECHNIQUE OF WILSON (WT)	75	71		
EXTERNAL AND VISCERAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Brain: Perimeningeal space, Red material (VIS)	1	0.01	0.00	0.60
Brain: Moderate dilation of lateral/third ventricles (VIS,WT)	3	0.02	0.00	0.63
Eye(s): Circumcornial hemorrhage (EXT)	8	0.07	0.00	1.13
Heart: Minor vessels: left common carotid merges into innominate (VIS)	1	0.01	0.00	0.62
Heart: Minor vessels; carotid/subclavian arteries arises from/merges into innominate artery (VIS)	1	0.01	0.00	0.59
Heart: Minor vessels; carotid/subclavian/innominate arteries merge into aortic arch/ascending aorta (VIS)	1	0.01	0.00	0.58
Heart: Minor vessels; extra vessel (VIS)	64	0.53	0.00	11.92
Heart: Minor vessels; innominate artery absent (VIS)	9	0.07	0.00	1.88
Heart: Minor vessels variation: malpositioned subclavian (VIS)	2	0.02	0.00	0.81
Heart: Subclavian narrowed (VIS)	1	0.01	0.00	0.52
Heart: Ventricle large (VIS)	1	0.01	0.00	0.57
Heart: Ventricle small (VIS) ‡‡	3	0.02	0.00	1.15
Lungs: Azygos/accessory lobe absent (VIS)	223	1.85	0.00	11.92
Lungs: Accessory lobe reduced (VIS)	1	0.01	0.00	0.51
Lungs: Cyst on accessory lobe (VIS)	1	0.01	0.00	0.56
Spleen: Reduced (VIS)	4	0.03	0.00	1.35
Spleen: Supernumerary (VIS)	2	0.02	0.00	0.64
Spleen: Discoloration (VIS)	1	0.01	0.00	0.52
Pancreas: Reduced (VIS)	1	0.01	0.00	0.68
Gallbladder: Absent (VIS)	23	0.19	0.00	1.55
Gallbladder: Small/Reduced (VIS)	2	0.02	0.00	0.70
Gallbladder: Supernumerary (VIS)	5	0.04	0.00	0.78
Liver: Lobe, Additional fissure (VIS)	3	0.02	0.00	0.60
Liver: Vestigial lobe (VIS)	32	0.27	0.00	4.60
Liver: Cyst (VIS)	1	0.01	0.00	0.61
Kidney(s): Pelvic kidney(s) (VIS)	2	0.02	0.00	0.65

* Study ranges, based on the group incidence

‡‡ Regraded in 2018

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
EXTERNAL AND VISCERAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Kidney(s): Absence of renal papillae (VIS)	2	0.02	0.00	0.61
Kidney(s): Renal papilla(e) small (VIS)	3	0.02	0.00	0.60
Kidney(s): Abnormal consistency solid white (VIS)	1	0.01	0.00	0.61
Adrenal gland: Accessory adrenal nodule present (VIS)	1	0.01	0.00	0.66
Abdomen: Abdominal distention (EXT)	1	0.01	0.00	0.52
Abdominal cavity: Cyst (VIS)	1	0.01	0.00	0.56
Abdominal/thoracic cavity: Excessive fluid present (ascites) (VIS)	1	0.01	0.00	0.53
Abdomen: Malpositioned umbilicus (EXT)	1	0.01	0.00	0.61
Testes: Cyst (VIS)	1	0.01	0.00	0.52
Urinary bladder: Distended (VIS)	1	0.01	0.00	0.53
Vein: Renal vein(s), Supernumerary (VIS)	4	0.03	0.00	2.07
Ureter(s): Retrocaval (VIS)	89	0.74	0.00	3.51
Ureter(s): Abnormal consistency solid white (VIS)	1	0.01	0.00	0.61
Ovary(ies): Cyst (VIS)	5	0.04	0.00	1.59
Tail: Kinked (EXT)	1	0.01	0.00	0.55
Gross exam: Subcutaneous edema (EXT)	2	0.02	0.00	0.55

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
SKELETAL (SKE)	Fetus examined 12045		Total no. of studies/groups used 71	
	Fetuses affected			
SKELETAL VARIATIONS	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Hyoid bone: Incomplete ossification	1304	10.83	0.00	43.50
[Hyoid bone: Irregular ossification]	27	0.22	0.00	3.49
Hyoid bone: Irregular ossification (misshapen)	237	1.97	0.00	6.31
Hyoid bone: Unossified [absent]	32	0.27	0.00	1.80
Hyoid bone: Bipartite	12	0.10	0.00	1.88
Hyoid bone: Semi-bipartite	73	0.61	0.00	12.50
Hyoid bone ala(e): Bent	127	1.05	0.00	5.18
Frontal bone(s): Incomplete ossification	1000	8.30	0.00	35.75
[Frontal bone(s): Irregular ossification]	1	0.01	0.00	0.68
Frontal bone(s): Fusion	3	0.02	0.00	0.65
Frontal/parietal bone(s): Unossified line	325	2.70	0.00	27.78
Frontal bone(s): Unossified area	2	0.02	0.00	0.57
Frontal bone(s): Misshapen	5	0.04	0.00	1.15
Frontal bone(s): Large	1	0.01	0.00	0.55
Parietal bone(s): Incomplete ossification	34	0.28	0.00	5.49
Parietal bone(s): Unossified area	1	0.01	0.00	0.55
Parietal bone(s): Misshapen	2	0.02	0.00	0.57
Parietal bone(s): Large	1	0.01	0.00	0.55
Interparietal bones: Incomplete ossification	12	0.10	0.00	2.07
Interparietal bones: Increased ossification	1	0.01	0.00	0.55
Interparietal bones: Malpositioned	1	0.01	0.00	0.55
Supraoccipital bone: Malpositioned	1	0.01	0.00	0.55
Supraoccipital bone: Reduced ossification	2	0.02	0.00	0.69
Supraoccipital bone: Incomplete ossification	5	0.04	0.00	2.21
Squamosal bone(s): Incomplete ossification	1	0.01	0.00	0.57
Nasal bone(s): Incomplete ossification [irregular]	50	0.42	0.00	2.87
Nasal bone and frontal bone: Fused, partial	2	0.02	0.00	0.57
Nasal bone(s): Unossified line	16	0.13	0.00	2.12
Nasal bone: Misshapen	2	0.02	0.00	0.57
Nasal bone: Suture, Malpositioned	1	0.01	0.00	0.54
Maxilla: Single incisor socket	1	0.01	0.00	0.53
Premaxilla: Incomplete ossification	2	0.02	0.00	0.61

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN				
Thoracic vertebral centrum: Incomplete ossification	13	0.11	0.00	1.20
Thoracic vertebral centrum: Semi-bipartite/dumbbell	826	6.86	0.00	12.64
Thoracic vertebral centrum: Bipartite	6	0.05	0.00	0.70
Thoracic vertebral centrum: Misaligned (includes malpositioned, displaced)	13	0.11	0.00	1.23
Thoracic vertebral centrum: Unossified	3	0.02	0.00	0.68
Thoracic vertebral centrum: Misshapen	2	0.02	0.00	0.57
Thoracic vertebral arch(es): Incomplete/reduced ossification	8	0.07	0.00	0.68
Thoracic vertebral arch(es): Ossification center	6	0.05	0.00	1.11
Caudal vertebra(e): Reduced no.	24	0.20	0.00	3.03
Caudal vertebra(e): Incomplete ossification	12	0.10	0.00	1.25
Caudal vertebra(e): Misaligned (includes malpositioned, displaced)	21	0.17	0.00	1.67
Caudal vertebra(e): Fused	3	0.02	0.00	0.56
Caudal vertebra(e): Bipartite	5	0.04	0.00	0.65
Cervical vertebra (1st): Incomplete ossification	30	0.25	0.00	5.99
Cervical vertebra (1st): Misshapen	1	0.01	0.00	0.60
Cervical vertebra: Ossification center	3	0.02	0.00	1.18
Cervical vertebral centrum: Misaligned (includes malpositioned)	5	0.04	0.00	0.81
Cervical vertebral centrum: Semi-bipartite/dumbbell	3	0.02	0.00	0.81
Cervical vertebral centrum: Bipartite	1	0.01	0.00	0.52
Cervical vertebral centrum: Incomplete/reduced ossification	31	0.26	0.00	3.95
Cervical vertebral centrum: Misshapen	1	0.01	0.00	0.52
Cervical vertebral centrum: Irregular ossification	1	0.01	0.00	0.59
Cervical vertebral arch(es): Incomplete/reduced ossification	4	0.03	0.00	0.68
Cervical vertebral arch(es): Unossified	1	0.01	0.00	0.64
Cervical vertebra arch(es): Ossification center	10	0.08	0.00	3.09
Lumbar vertebra: Ossification center	12	0.10	0.00	2.21
Lumbar vertebral centrum: Misaligned (includes malpositioned)	5	0.04	0.00	1.08
Lumbar vertebral arch(es): Incomplete ossification	1	0.01	0.00	0.59
Lumbar vertebral arch(es): Irregular ossification	1	0.01	0.00	0.59
Lumbar vertebral arch(es): Misaligned	1	0.01	0.00	0.78
Lumbar vertebral arch(es): Ossification center	10	0.08	0.00	1.61
Lumbar vertebral centrum: Absent	1	0.01	0.00	0.78
Lumbar vertebral centrum: Bipartite	1	0.01	0.00	0.56
Lumbar vertebral centrum: Semi-bipartite	1	0.01	0.00	0.61
Lumbar vertebral centrum: Incomplete ossification	2	0.02	0.00	0.59

* Study ranges, based on the group incidence

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RABBIT NZW (Hra: [NZW] SPF), 2007 – 2018[@]
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CONT'D)				
1st Lumbar centrum fused with 13th thoracic centrum	1	0.01	0.00	0.56
Sacral vertebral centrum: Incomplete ossification	1	0.01	0.00	0.61
Sacral vertebra(e): Irregular ossification	1	0.01	0.00	0.59
Sacral vertebral arch(es): Incomplete ossification	5	0.04	0.00	2.35
Extra pre-sacral vertebrae	36	0.30	0.00	3.31
25 pre-sacral vertebrae	9	0.07	0.00	1.23
Ossification center(s) on 1st lumbar vertebra	41	0.34	0.00	2.33
RIBS				
Nodulated	20	0.17	0.00	1.85
Reduced (Incomplete ossification)	8	0.07	0.00	1.14
Bifurcated	1	0.01	0.00	0.62
Misaligned (displaced)	1	0.01	0.00	0.70
Misshapen	2	0.02	0.00	0.60
Short	1	0.01	0.00	0.53
Cervical, Full	2	0.02	0.00	0.58
Cervical, Short	19	0.16	0.00	3.70
Ossification center(s) on 7th cervical vertebra	66	0.55	0.00	6.22
Rib(s) on 7th cervical vertebra	64	0.53	0.00	4.03
Malpositioned	1	0.01	0.00	0.55
Ossification center(s) on 1st cervical vertebra	1	0.01	0.00	0.60
Interrupted rib(s)	5	0.04	0.00	0.78
Rib 13th, full (extra) (unilateral/bilateral)	956	7.94	0.00	50.00
Rib 13th, short (rudimentary) (unilateral/bilateral)	490	4.07	0.00	28.33
STERNEBRAL COLUMN				
Fused	169	1.40	0.00	4.15
Misaligned	5	0.04	0.00	0.64
Extra sternebra(e)/extra ossification in sternebral column	204	1.69	0.00	7.04
Bifurcated/misshapen	31	0.26	0.00	6.90
Incomplete ossification	880	7.31	0.00	48.85
Increased ossification	1	0.01	0.00	0.55
Unossified	472	3.92	0.00	27.18
Bipartite ossification	44	0.37	0.00	5.38
Dumbbell ossification /semi-bipartite	16	0.13	0.00	2.92

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	116	0.96	0.00	5.23
Pubic bone(s): Absent/unossified	7	0.06	0.00	0.81
LIMBS				
Scapula(e): Misshapen	1	0.01	0.00	0.55
Reduced no. of phalange(s) in pollex(ices)	8	0.07	0.00	0.63
Reduced no. of tarsal bones	2	0.02	0.00	0.61
Reduced no. of bones in forepaw(s)	2	0.02	0.00	0.59
Reduced no. of phalange(s) in forepaw(s)	12	0.10	0.00	1.84
Reduced no. of phalange(s) in hindpaw(s)	1	0.01	0.00	0.58
Forepaw(s): Phalange(s) misshapen	3	0.02	0.00	1.18
Clavicle(s): Incomplete ossification	1	0.01	0.00	0.57
Hindpaw(s): Irregular ossification	5	0.04	0.00	0.65
Forepaw(s): Irregular ossification	28	0.23	0.00	4.55
Forepaw(s): Phalange(s) incomplete ossification	5	0.04	0.00	1.67
Hindlimb: Tarsal bone increased ossification	1	0.01	0.00	0.52
Hindlimb: Tarsal bone unossified	2	0.02	0.00	1.04
Hindlimb: Tarsal bone incomplete ossification	8	0.07	0.00	2.59
Forelimb: Ulna thin	1	0.01	0.00	0.55

* Study ranges, based on the group incidence

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP MATERNAL FINDINGS			
Parameter	Total	Minimum*	Maximum*
No. of Does Inseminated / Mated	236	12	22
No. of Does Pregnant	221	11	22
No. of Does Pregnant by Ammonium Sulfide Staining	0	0	0
No. of Does with Abortion	1	0	1
Abortion Rate (%)	-	0.0	4.8
No. of Does Littering Early	0	0	0
No. of Does with Live Fetuses	217	11	22
No. of Does with Total Litter Death / Resorption	3	0	1
No. of Does Dying or Unscheduled Euthanasia on Study	4	0	1
Mortality Rate (%)	-	0.0	5.0
Pregnancy Rate (%)	-	81.8	100.0

EMBRYO-FETAL DEVELOPMENT STUDIES			
GROUP OVARIAN AND UTERINE FINDINGS			
Parameter	Average	Minimum*	Maximum*
Corpora Lutea / Doe	11.7	10.7	12.8
Total Implantation Sites / Litter	11.0	9.5	11.8
Sex Ratio (% Males) / Litter	51.1	43.9	55.6
Total Live Fetuses / Litter	10.4	9.1	11.1
Dead Fetuses / Litter	0.0	0.0	0.0
Early Resorptions / Litter	0.3	0.1	1.0
Late Resorptions / Litter	0.3	0.1	0.5
Total Resorptions / Litter	0.6	0.1	1.1
Pre-Implantation Loss (%) / Litter	6.8	2.8	14.4
Post-Implantation Loss (%) / Litter	4.9	1.3	9.1

* Study ranges, based on the group incidence, group percentage or group mean

[@] The year (s) dosing was initiated on the studies

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EMBRYO-FETAL DEVELOPMENT STUDIES			
FETAL WEIGHTS - SUMMARY DATA			
Parameter	Average	Minimum*	Maximum*
Fetal Weight (g) - Males	40.4	37.5	42.9
Fetal Weight (g) - Females	39.3	36.9	41.4
Fetal Weight (g) - Total	39.9	37.2	42.1

* Study ranges, based on the group incidence, group percentage or group mean

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters examined			
EXTERNAL (EXT)	215	Total no. of		
VISCERAL (VIS)	215	studies/groups used		
SKELETAL (SKE)	215	12		
	Litters affected			
MALFORMATIONS	SUM	AVERAGE %	MIN %*	MAX %*
Head: Anencephaly (EXT)	1	0.47	0.00	5.26
Cranium: Meningoencephalocele (EXT)	1	0.47	0.00	4.55
Skull: Basioccipital bone, absent (SKE)	1	0.47	0.00	5.26
Skull: Basisphenoid bone, absent (SKE)	1	0.47	0.00	5.26
Skull: Exoccipital bone, absent (SKE)	1	0.47	0.00	5.26
Skull: Frontal bone, absent (SKE)	1	0.47	0.00	5.26
Skull: Premaxilla small (SKE)	1	0.47	0.00	5.88
Skull: Premaxilla absent (SKE)	1	0.47	0.00	5.26
Skull: Interparietal, absent (SKE)	1	0.47	0.00	5.26
Skull: Mandible absent (SKE)	1	0.47	0.00	5.26
Skull: Maxilla absent (SKE)	1	0.47	0.00	5.26
Skull: Nasal bone(s) absent (SKE)	1	0.47	0.00	5.26
Skull: Palatine bone(s) absent (SKE)	1	0.47	0.00	5.26
Skull: Parietal bone(s) absent (SKE)	1	0.47	0.00	5.26
Skull: Squamosal bone(s) absent (SKE)	1	0.47	0.00	5.26
Skull: Supraoccipital bone(s) absent (SKE)	1	0.47	0.00	5.26
Skull: Maxilla short confirmed (SKE)	1	0.47	0.00	4.55
Skull: Mandible short confirmed (SKE)	1	0.47	0.00	4.55
Hyoid bone: Absent (SKE)	2	0.93	0.00	10.53
Eye(s): Eye(s) small (VIS)	1	0.47	0.00	4.55
Eye(s): Bulge(s) small (microphthalmia) (EXT)	1	0.47	0.00	5.26
Eye(s): Opacity (EXT)	1	0.47	0.00	6.25
Face: Lower jaw small/reduced (mandibular micrognathia) (EXT)	1	0.47	0.00	4.55
Face: Upper jaw small/reduced (maxillary micrognathia) (EXT)	1	0.47	0.00	4.55
Face: Cleft lip (EXT)	1	0.47	0.00	4.55
Face: Naris, Malpositioned (EXT)	1	0.47	0.00	5.88
Heart: Dilatation of the ascending aorta (VIS)	4	1.86	0.00	10.53
Heart: Dilatation of aortic arch (VIS)	3	1.40	0.00	5.88
Heart: Stenosis of pulmonary trunk (VIS)	3	1.40	0.00	10.53
Heart: Ventricular septum absent (VIS)	2	0.93	0.00	5.26
Heart: Ventricular septum defect (VIS)	6	2.79	0.00	10.53
Heart: Minor vessels: Retroesophageal subclavian artery (VIS)	2	0.93	0.00	11.76
Heart: Heart misshapen (cardiomegaly) (VIS)	2	0.93	0.00	5.26
Heart: Persistent truncus arteriosus (Common truncus) (VIS)	4	1.86	0.00	5.88
Heart: Ventricular wall, Thick (VIS)	1	0.47	0.00	5.56

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Lungs: Lobe(s) small/reduced (VIS)	1	0.47	0.00	4.55
Lungs: Caudal lobe(s) absent (VIS)	1	0.47	0.00	4.55
Liver: Supernumerary lobe(s) (VIS)	1	0.47	0.00	5.00
Vertebral column: Caudal vertebra, Absent (SKE)	1	0.47	0.00	5.88
Vertebral column: Lumbar arch(es), Splayed (open) (SKE)	1	0.47	0.00	5.56
Vertebral column: Lumbar vertebra: Absent (SKE)	1	0.47	0.00	5.88
Vertebral column: Sacral vertebra: Absent (SKE)	1	0.47	0.00	5.88
Vertebral column: Thoracic vertebral arch(es), Absent (SKE) ‡‡	10	4.65	0.00	18.18
Vertebral column: Thoracic vertebral arch(es), Fused (SKE)	1	0.47	0.00	5.88
Vertebral column: Thoracic vertebral centra, Absent (SKE) ‡‡	4	1.86	0.00	9.09
Vertebral column: Thoracic vertebral centra, Fused (SKE) ‡‡	3	1.40	0.00	9.09
Vertebral column: Lumbar vertebral arch(es): Absent/unossified (SKE) ‡	4	1.86	0.00	8.33
Ribs: Absent (SKE) ‡‡	4	1.86	0.00	9.09
Ribs: Branched (SKE) ‡‡	2	0.93	0.00	9.09
Ribs: Fused (SKE) ‡‡	3	1.40	0.00	9.09
Thorax/vertebral column: Spina bifida (EXT,SKE)	1	0.47	0.00	5.56
Abdomen: Abdominal muscles herniated (EXT)	2	0.93	0.00	5.88
Abdomen: Intestines protruding at umbilicus (omphalocele) (EXT)	1	0.47	0.00	5.26
Kidney(s): Fused (VIS)	1	0.47	0.00	5.88
Kidney(s): Kidney(s) small (VIS)	2	0.93	0.00	4.55
Kidney(s): Malpositioned (VIS)	5	2.33	0.00	9.09
Trunk: Gastroschisis (EXT)	1	0.47	0.00	5.26
Trunk: Distended abdomen (EXT)	1	0.47	0.00	5.26
Trunk: Short (Microcormia) (EXT)	1	0.47	0.00	5.88
Trunk: Anus, small (EXT)	1	0.47	0.00	5.88
Tail: Microcaudia (EXT)	2	0.93	0.00	5.88
Limb(s): Abnormal flexure/articulationof forelimb(s) (EXT)	5	2.33	0.00	11.76
Limb(s): Abnormal flexure/hyperflexure/hyperextension of hindlimb(s) (EXT)	3	1.40	0.00	5.88
Limb(s): Abnormal flexure of hindpaw(s) (EXT)	1	0.47	0.00	4.55
Limb(s): Hindlimb malrotated (EXT)	3	1.40	0.00	5.88
Limb(s): Inward malrotation of forepaw(s) (EXT)	1	0.47	0.00	4.55
Limb(s): Outward malrotation of forepaw(s) (EXT)	1	0.47	0.00	4.55
Limb(s): Outward malrotation of hindpaw(s) (EXT)	1	0.47	0.00	4.55
Limb(s): Malpositioned pollex (EXT)	1	0.47	0.00	4.55

* Study ranges, based on the group incidence
‡ Regraded in 2017
‡‡ Regraded in 2018

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
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EMBRYO-FETAL DEVELOPMENT STUDIES

GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS
MALFORMATIONS AND VARIATIONS

	Litters affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Limb(s): Forelimb(s) thin (EXT)	1	0.47	0.00	4.55
Limb(s): Ulna misaligned (SKE)	1	0.47	0.00	4.55
Limb(s): Ulna irregular ossification (SKE)	1	0.47	0.00	4.55
Limb(s): Displaced pollex (SKE)	1	0.47	0.00	4.55

* Study ranges, based on the group incidence

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL AND VISCERAL VARIATIONS	Litters affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Brain: Moderate dilation of lateral/third ventricles (VIS)	1	0.47	0.00	5.88
Eye(s): Circumcornial hemorrhage (EXT)	4	1.86	0.00	6.25
Heart: Minor vessels; extra vessel (VIS)	3	1.40	0.00	5.56
Heart: Atrium small (VIS)	1	0.47	0.00	4.55
Vein: Renal vein, supernumerary (VIS)	4	1.86	0.00	21.05
Lungs: Azygos/accessory lobe absent (VIS)	18	8.37	0.00	15.79
Gallbladder: Absent (VIS)	1	0.47	0.00	6.25
Gallbladder: Small/reduced (VIS)	1	0.47	0.00	5.26
Gallbladder: Supernumerary (VIS)	1	0.47	0.00	5.88
Gallbladder: Bilobed (VIS)	2	0.93	0.00	5.26
Liver: Lobe(s) misshapen (VIS)	1	0.47	0.00	5.88
Liver: Liver lobe(s) vestigial (VIS)	1	0.47	0.00	5.26
Liver: Supernumerary lobe/Vestigial lobe (VIS)	3	1.40	0.00	10.00
Liver: Lobe, large (VIS)	1	0.47	0.00	5.00
Kidney(s): Renal papilla(e) small, moderate (VIS)	1	0.47	0.00	5.00
Abdominal cavity: Small stomach (VIS)	1	0.47	0.00	4.55
Abdominal cavity: Stomach content discolored dark (VIS)	2	0.93	0.00	9.09
Spleen: Spleen split/fragmented (VIS)	1	0.47	0.00	5.26
Spleen: Spleen small (VIS)	1	0.47	0.00	4.55
Ureter(s): Retrocaval (VIS)	11	5.12	0.00	25.00
Ureter(s): Ureter(s) malrotated (VIS)	1	0.47	0.00	4.55
Ovary(ies): Cyst (VIS)	2	0.93	0.00	5.88
Limb(s): Abnormal flexure of forepaw(s) (EXT)	2	0.93	0.00	4.55
General: Abdomen, Fluid-filled (VIS)	1	0.47	0.00	5.88

* Study ranges, based on the group incidence

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CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Hyoid bone: Incomplete ossification	75	34.88	10.53	55.00
Hyoid bone: Irregular ossification (misshapen)	7	3.26	0.00	15.79
Hyoid bone: Unossified	19	8.84	0.00	22.73
Hyoid bone: Bipartite	2	0.93	0.00	10.53
Hyoid bone: Semi-bipartite	14	6.51	0.00	52.63
Hyoid bone ala(e): Bent	7	3.26	0.00	25.00
Frontal bone(s): Incomplete ossification	65	30.23	0.00	72.73
Frontal bone(s): Unossified line	63	29.30	0.00	89.47
Frontal bone(s): Unossified area	1	0.47	0.00	5.00
Parietal bone(s): Unossified area	1	0.47	0.00	5.88
Parietal bone(s): Incomplete ossification	2	0.93	0.00	11.11
Interparietal bone: Incomplete ossification	2	0.93	0.00	5.56
Supraoccipital bone: Incomplete ossification	1	0.47	0.00	4.55
Nasal bone(s): Incomplete ossification	15	6.98	0.00	21.05
Nasal bone(s): Unossified line	7	3.26	0.00	15.79
Single incisor socket	1	0.47	0.00	5.88
VERTEBRAL COLUMN				
Thoracic vertebral centrum: Incomplete ossification	5	2.33	0.00	10.00
[Thoracic vertebral centrum: Irregular ossification]	1	0.47	0.00	5.26
Thoracic vertebral centrum: Semi-bipartite/dumbbell	95	44.19	18.18	63.16
Thoracic vertebral centrum: Bipartite	1	0.47	0.00	5.00
Thoracic vertebral centrum: Misaligned (includes malpositioned, displaced)	7	3.26	0.00	11.76
Thoracic vertebral centra: Fused	2	0.93	0.00	9.09
Thoracic vertebral arch(es): Misshapen	1	0.47	0.00	5.88
Thoracic vertebral centrum: Misshapen	2	0.93	0.00	5.88
Thoracic vertebral arch(es): Ossification center	2	0.93	0.00	5.26
Caudal vertebra(e): Reduced no.	4	1.86	0.00	5.88
Caudal vertebra(e): Incomplete ossification	3	1.40	0.00	5.88
Caudal vertebra(e): Misaligned (includes malpositioned, displaced)	6	2.79	0.00	10.53
Caudal vertebra(e): Misshapen	1	0.47	0.00	5.56
Cervical vertebral centra: Fused	1	0.47	0.00	4.55
Cervical vertebral centrum: Malpositioned	1	0.47	0.00	4.55
Cervical vertebral centrum: Bipartite	1	0.47	0.00	5.26
Cervical vertebral centrum: Incomplete/reduced ossification	8	3.72	0.00	29.41
Cervical vertebral centrum: Absent/unossified	1	0.47	0.00	4.55

* Study ranges, based on the group incidence

[@] The year (s) dosing was initiated on the studies

HISTORICAL CONTROL DATA
RABBIT NZW (Crl: KBL [NZW]), 2009 - 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CONT'D)				
Cervical vertebra arch(es): Ossification center	3	1.40	0.00	15.00
Cervical vertebral arch(es): Absent/unossified	1	0.47	0.00	4.55
Lumbar vertebral centrum: Misaligned (includes malpositioned)	3	1.40	0.00	8.33
Lumbar vertebral centrum: Bipartite	1	0.47	0.00	5.26
Lumbar vertebral centrum: Incomplete ossification	2	0.93	0.00	5.56
Lumbar vertebral arch(es): Ossification center	5	2.33	0.00	10.00
Extra pre-sacral vertebrae	2	0.93	0.00	9.09
25 pre-sacral vertebrae	2	0.93	0.00	9.09
Ossification center(s) on 1st lumbar vertebra	2	0.93	0.00	9.09
RIBS				
Thickened	1	0.47	0.00	5.88
Nodulated	2	0.93	0.00	5.26
Detached	1	0.47	0.00	5.26
Cervical, Short	2	0.93	0.00	5.88
Ossification center(s) on 7th cervical vertebra	2	0.93	0.00	4.55
Rib(s) on 7th cervical vertebra	4	1.86	0.00	13.64
Misshapen	1	0.47	0.00	5.26
Interrupted	5	2.33	0.00	12.50
Rib 13th extra (full) (unilateral/bilateral)	90	41.86	0.00	90.00
Rib 13th rudimentary (short) (unilateral/bilateral)	72	33.49	0.00	85.00
STERNEBRAL COLUMN				
Bipartite ossification	8	3.72	0.00	20.00
Semi-bipartite/dumbbell ossification	10	4.65	0.00	35.00
Incomplete ossification	96	44.65	0.00	100.00
Increased ossification	1	0.47	0.00	5.00
Fused	26	12.09	0.00	31.25
Unossified	76	35.35	0.00	80.00
Misaligned	4	1.86	0.00	10.53
Extra sternebra(e)/extra ossification in sternebral column	5	2.33	0.00	5.56
Bifurcated/misshapen	11	5.12	0.00	25.00

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Litters affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	14	6.51	0.00	23.53
Pubic bone(s): Absent/unossified	6	2.79	0.00	11.76
LIMBS				
Tarsal bone: Incomplete ossification	6	2.79	0.00	17.65
Reduced no. of phalange(s) in pollex(ices)	3	1.40	0.00	5.26
Reduced no. of phalange(s) in tarsal(s)	1	0.47	0.00	4.55
Reduced no. of phalange(s) in forepaw(s)	2	0.93	0.00	5.26
Reduced no. of phalange(s) in hindpaw(s)	2	0.93	0.00	10.53
Clavicle(s): Misshapen	2	0.93	0.00	10.53

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CHARLES RIVER LABORATORIES MONTREAL
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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses examined			
EXTERNAL (EXT)	2248	Total no. of		
VISCERAL (VIS)	2247	studies/groups used		
SKELETAL (SKE)	2248	12		
	Fetuses affected			
MALFORMATIONS	SUM	AVERAGE %	MIN %*	MAX %*
Head: Anencephaly (EXT)	1	0.04	0.00	0.50
Cranium: Meningoencephalocele (EXT)	1	0.04	0.00	0.42
Skull: Basioccipital bone, absent (SKE)	1	0.04	0.00	0.50
Skull: Basisphenoid bone, absent (SKE)	1	0.04	0.00	0.50
Skull: Exoccipital bone, absent (SKE)	1	0.04	0.00	0.50
Skull: Frontal bone, absent (SKE)	1	0.04	0.00	0.50
Skull: Premaxilla small (SKE)	1	0.04	0.00	0.61
Skull: Premaxilla absent (SKE)	1	0.04	0.00	0.50
Skull: Interparietal, absent (SKE)	1	0.04	0.00	0.50
Skull: Mandible absent (SKE)	1	0.04	0.00	0.50
Skull: Maxilla absent (SKE)	1	0.04	0.00	0.50
Skull: Nasal bone(s) absent (SKE)	1	0.04	0.00	0.50
Skull: Palatine bone(s) absent (SKE)	1	0.04	0.00	0.50
Skull: Parietal bone(s) absent (SKE)	1	0.04	0.00	0.50
Skull: Squamosal bone(s) absent (SKE)	1	0.04	0.00	0.50
Skull: Supraoccipital bone(s) absent (SKE)	1	0.04	0.00	0.50
Skull: Maxilla short confirmed (SKE)	1	0.04	0.00	0.42
Skull: Mandible short confirmed (SKE)	1	0.04	0.00	0.42
Hyoid bone: Absent (SKE)	2	0.09	0.00	1.01
Eye(s): Eye(s) small (VIS)	1	0.04	0.00	0.42
Eye(s): Bulge(s) small (microphthalmia) (EXT)	2	0.09	0.00	1.00
Eye(s): Opacity (EXT)	1	0.04	0.00	0.56
Face: Lower jaw small/reduced (mandibular micrognathia) (EXT)	1	0.04	0.00	0.42
Face: Upper jaw small/reduced (maxillary micrognathia) (EXT)	1	0.04	0.00	0.42
Face: Cleft lip (EXT)	1	0.04	0.00	0.42
Face: Naris, Malpositioned (EXT)	1	0.04	0.00	0.61
Heart: Dilatation of the ascending aorta (VIS)	4	0.18	0.00	1.00
Heart: Dilatation of aortic arch (VIS)	3	0.13	0.00	0.61
Heart: Stenosis of pulmonary trunk (VIS)	3	0.13	0.00	1.00
Heart: Ventricular septum absent (VIS)	2	0.09	0.00	0.50
Heart: Ventricular septum defect (VIS)	6	0.27	0.00	1.00
Heart: Minor vessels: Retroesophageal subclavian artery (VIS)	2	0.09	0.00	1.22
Heart: Heart misshapen (cardiomegaly) (VIS)	2	0.09	0.00	0.50
Heart: Persistent truncus arteriosus (Common truncus) (VIS)	4	0.18	0.00	0.61
Heart: Ventricular wall, Thick (VIS)	1	0.04	0.00	0.56
Lungs: Lobe(s) small/reduced (VIS)	1	0.04	0.00	0.42
Lungs: Caudal lobe(s) absent (VIS)	1	0.04	0.00	0.42
Liver: Supernumerary lobe(s) (VIS)	1	0.04	0.00	0.54

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CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
MALFORMATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
Vertebral column: Caudal vertebra, Absent (SKE)	1	0.04	0.00	0.61
Vertebral column: Lumbar arch(es), Splayed (open) (SKE)	1	0.04	0.00	0.56
Vertebral column: Lumbar vertebra: Absent (SKE)	1	0.04	0.00	0.61
Vertebral column: Sacral vertebra: Absent (SKE)	1	0.04	0.00	0.61
Vertebral column: Thoracic vertebral arch(es), Absent (SKE) ‡‡	10	0.44	0.00	1.69
Vertebral column: Thoracic vertebral arch(es), Fused (SKE)	1	0.04	0.00	0.61
Vertebral column: Thoracic vertebral centra, Absent (SKE) ‡‡	4	0.18	0.00	0.85
Vertebral column: Thoracic vertebral centra, Fused (SKE) ‡‡	3	0.13	0.00	0.85
Vertebral column: Lumbar vertebral arch(es): Absent/unossified (SKE) ‡	4	0.18	0.00	0.79
Ribs: Absent (SKE) ‡‡	4	0.18	0.00	0.85
Ribs: Branched (SKE) ‡‡	2	0.09	0.00	0.85
Ribs: Fused (SKE) ‡‡	4	0.18	0.00	1.69
Thorax/vertebral column: Spina bifida (EXT,SKE)	1	0.04	0.00	0.56
Abdomen: Abdominal muscles herniated (EXT)	2	0.09	0.00	0.61
Abdomen: Intestines protruding at umbilicus (omphalocele) (EXT)	1	0.04	0.00	0.50
Kidney(s): Fused (VIS)	1	0.04	0.00	0.61
Kidney(s): Kidney(s) small (VIS)	2	0.09	0.00	0.42
Kidney(s): Malpositioned (VIS)	5	0.22	0.00	0.84
Trunk: Gastroschisis (EXT)	1	0.04	0.00	0.50
Trunk: Distended abdomen (EXT)	1	0.04	0.00	0.50
Trunk: Short (Microcormia) (EXT)	1	0.04	0.00	0.61
Trunk: Anus, small (EXT)	1	0.04	0.00	0.61
Tail: Microcaudia (EXT)	2	0.09	0.00	0.61
Limb(s): Abnormal flexure/articulation of forelimb(s) (EXT)	5	0.22	0.00	1.22
Limb(s): Abnormal flexure/hyperflexure/hyperextension of hindlimb(s) (EXT)	3	0.13	0.00	0.61
Limb(s): Abnormal flexure of hindpaw(s) (EXT)	1	0.04	0.00	0.42
Limb(s): Hindlimb malrotated (EXT)	3	0.13	0.00	0.61
Limb(s): Inward malrotation of forepaw(s) (EXT)	1	0.04	0.00	0.42
Limb(s): Outward malrotation of forepaw(s) (EXT)	1	0.04	0.00	0.42
Limb(s): Outward malrotation of hindpaw(s) (EXT)	1	0.04	0.00	0.42
Limb(s): Malpositioned pollex (EXT)	1	0.04	0.00	0.42
Limb(s): Forelimb(s) thin (EXT)	1	0.04	0.00	0.42
Limb(s): Ulna misaligned (SKE)	1	0.04	0.00	0.42
Limb(s): Ulna irregular ossification (SKE)	1	0.04	0.00	0.42
Limb(s): Displaced pollex (SKE)	1	0.04	0.00	0.42

* Study ranges, based on the group incidence
‡ Regraded in 2017
‡‡ Regraded in 2018

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HISTORICAL CONTROL DATA
RABBIT NZW (Crl: KBL [NZW]), 2009 - 2018[@]
CHARLES RIVER LABORATORIES MONTREAL
ALL ROUTES OF ADMINISTRATION

EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
EXTERNAL AND VISCERAL VARIATIONS	Fetuses affected			
	SUM	AVERAGE %	MIN %*	MAX %*
Brain: Moderate dilation of lateral/third ventricles (VIS)	1	0.04	0.00	0.61
Eye(s): Circumcornial hemorrhage (EXT)	4	0.18	0.00	0.56
Heart: Minor vessels; extra vessel (VIS)	3	0.13	0.00	0.56
Heart: Atrium small (VIS)	1	0.04	0.00	0.42
Vein: Renal vein, supernumerary (VIS)	4	0.18	0.00	2.01
Lungs: Azygos/accessory lobe absent (VIS)	22	0.98	0.00	2.69
Gallbladder: Absent (VIS)	1	0.04	0.00	0.56
Gallbladder: Small/reduced (VIS)	1	0.04	0.00	0.50
Gallbladder: Supernumerary (VIS)	1	0.04	0.00	0.61
Gallbladder: Bilobed (VIS)	2	0.09	0.00	0.50
Liver: Lobe(s) misshapen (VIS)	1	0.04	0.00	0.61
Liver: Liver lobe(s) vestigial (VIS)	1	0.04	0.00	0.50
Liver: Supernumerary lobe/Vestigial lobe (VIS)	5	0.22	0.00	2.15
Liver: Lobe, large (VIS)	1	0.04	0.00	0.54
Kidney(s): Renal papilla(e) small, moderate (VIS)	1	0.04	0.00	0.54
Abdominal cavity: Small stomach (VIS)	1	0.04	0.00	0.42
Abdominal cavity: Stomach content discolored dark (VIS)	3	0.13	0.00	1.27
Spleen: Spleen split/fragmented (VIS)	1	0.04	0.00	0.50
Spleen: Spleen small (VIS)	1	0.04	0.00	0.42
Ureter(s): Retrocaval (VIS)	17	0.76	0.00	3.76
Ureter(s): Ureter(s) malrotated (VIS)	1	0.04	0.00	0.42
Ovary(ies): Cyst (VIS)	2	0.09	0.00	0.61
Limb(s): Abnormal flexure of forepaw(s) (EXT)	2	0.09	0.00	0.42
General: Abdomen, Fluid-filled (VIS)	1	0.04	0.00	0.61

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GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
SKELETAL VARIATIONS	SUM	AVERAGE %	MIN %*	MAX %*
SKULL				
Hyoid bone: Incomplete ossification	179	7.96	1.00	22.03
Hyoid bone: Irregular ossification (misshapen)	8	0.36	0.00	2.01
Hyoid bone: Unossified	23	1.02	0.00	2.44
Hyoid bone: Bipartite	3	0.13	0.00	1.49
Hyoid bone: Semi-bipartite	37	1.65	0.00	15.92
Hyoid bone ala(e): Bent	9	0.40	0.00	3.23
Frontal bone(s): Incomplete ossification	107	4.76	0.00	12.71
Frontal bone(s): Unossified line	114	5.07	0.00	21.61
Frontal bone(s): Unossified area	1	0.04	0.00	0.45
Parietal bone(s): Unossified area	1	0.04	0.00	0.61
Parietal bone(s): Incomplete ossification	2	0.09	0.00	1.12
Interparietal bone: Incomplete ossification	2	0.09	0.00	0.56
Supraoccipital bone: Incomplete ossification	1	0.04	0.00	0.42
Nasal bone(s): Incomplete ossification	20	0.89	0.00	3.98
Nasal bone(s): Unossified line	7	0.31	0.00	1.51
Single incisor socket	1	0.04	0.00	0.61
VERTEBRAL COLUMN				
Thoracic vertebral centrum: Incomplete ossification	7	0.31	0.00	2.54
[Thoracic vertebral centrum: Irregular ossification]	1	0.04	0.00	0.50
Thoracic vertebral centrum: Semi-bipartite/dumbbell	206	9.16	1.69	16.92
Thoracic vertebral centrum: Bipartite	1	0.04	0.00	0.54
Thoracic vertebral centrum: Misaligned (includes malpositioned, displaced)	7	0.31	0.00	1.22
Thoracic vertebral centra: Fused	2	0.09	0.00	0.85
Thoracic vertebral arch(es): Misshapen	1	0.04	0.00	0.61
Thoracic vertebral centrum: Misshapen	2	0.09	0.00	0.61
Thoracic vertebral arch(es): Ossification center	2	0.09	0.00	0.50
Caudal vertebra(e): Reduced no.	6	0.27	0.00	1.27
Caudal vertebra(e): Incomplete ossification	5	0.22	0.00	1.12
Caudal vertebra(e): Misaligned (includes malpositioned, displaced)	8	0.36	0.00	1.12
Caudal vertebra(e): Misshapen	1	0.04	0.00	0.56
Cervical vertebral centra: Fused	1	0.04	0.00	0.42
Cervical vertebral centrum: Malpositioned	1	0.04	0.00	0.42
Cervical vertebral centrum: Bipartite	1	0.04	0.00	0.50
Cervical vertebral centrum: Incomplete/reduced ossification	8	0.36	0.00	3.05
Cervical vertebral centrum: Absent/unossified	1	0.04	0.00	0.42
Cervical vertebra arch(es): Ossification center	4	0.18	0.00	1.80
Cervical vertebral arch(es): Absent/unossified	1	0.04	0.00	0.42
Lumbar vertebral centrum: Misaligned (includes malpositioned)	3	0.13	0.00	0.79

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EMBRYO-FETAL DEVELOPMENT STUDIES				
GROUP INCIDENCE OF FETAL EXTERNAL, VISCERAL AND SKELETAL FINDINGS MALFORMATIONS AND VARIATIONS				
	Fetuses affected			
SKELETAL VARIATIONS (CONT'D)	SUM	AVERAGE %	MIN %*	MAX %*
VERTEBRAL COLUMN (CONT'D)				
Lumbar vertebral centrum: Bipartite	1	0.04	0.00	0.50
Lumbar vertebral centrum: Incomplete ossification	2	0.09	0.00	0.56
Lumbar vertebral arch(es): Ossification center	5	0.22	0.00	1.08
Extra pre-sacral vertebrae	2	0.09	0.00	0.85
25 pre-sacral vertebrae	2	0.09	0.00	0.85
Ossification center(s) on 1st lumbar vertebra	2	0.09	0.00	0.85
RIBS				
Thickened	1	0.04	0.00	0.61
Nodulated	2	0.09	0.00	0.50
Detached	1	0.04	0.00	0.50
Cervical, Short	4	0.18	0.00	1.83
Ossification center(s) on 7th cervical vertebra	2	0.09	0.00	0.42
Rib(s) on 7th cervical vertebra	5	0.22	0.00	1.68
Misshapen	1	0.04	0.00	0.50
Interrupted	5	0.22	0.00	1.12
Rib 13th extra (full) (unilateral/bilateral)	342	15.21	0.00	39.78
Rib 13th rudimentary (short) (unilateral/bilateral)	144	6.41	0.00	17.12
STERNEBRAL COLUMN				
Bipartite ossification	9	0.40	0.00	2.69
Semi-bipartite/dumbbell ossification	11	0.49	0.00	4.30
Incomplete ossification	365	16.24	0.00	45.23
Increased ossification	1	0.04	0.00	0.45
Fused	35	1.56	0.00	3.60
Unossified	247	10.99	0.00	30.65
Misaligned	4	0.18	0.00	1.01
Extra sternebra(e)/extra ossification in sternebral column	6	0.27	0.00	1.08
Bifurcated/misshapen	17	0.76	0.00	4.95
PELVIC GIRDLE				
Pubic bone(s): Incomplete ossification	19	0.85	0.00	4.88
Pubic bone(s): Absent/unossified	7	0.31	0.00	1.83
LIMBS				
Tarsal bone: Incomplete ossification	8	0.36	0.00	3.05
Reduced no. of phalange(s) in pollex(ices)	4	0.18	0.00	0.85
Reduced no. of phalange(s) in tarsal(s)	1	0.04	0.00	0.42
Reduced no. of phalange(s) in forepaw(s)	3	0.13	0.00	0.85
Reduced no. of phalange(s) in hindpaw(s)	2	0.09	0.00	0.99
Clavicle(s): Misshapen	2	0.09	0.00	1.01

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